REMARKS

NEW CLAIM

Applicants respectfully request that new claim 79 be entered into the record. It does not present new matter.

OATH/DECLARATION

Applicant respectfully brings to the attention of the Examiner that Arntzen is an inventor who either refuses to sign or cannot be reached by persons authorized under 37 C.F.R. § 1.47. This box was checked and previously submitted with a declaration. Applicants are enclosing a photocopy of the "Transmittal of Combined Declaration and Power of Attorney of Charles J. Arntzen", which demonstrates this. Applicants respectfully request that if the statement regarding the inventor's availability or refusal to sign is not present in the file, that it be entered into the record.

CLAIM OBJECTIONS

The Examiner states:

> Claims 75 and 75 are objected to because of the following informalities: Claims 74 and 75 recite the phrases "said plant is tomato" and "said plant is potato". Said phrasing, while interpretable, could be confusing. It is suggested that the aforementioned phrases be changed to "said plant is a tomato plant" and "said plant is a potato plant".

PTO Paper No. 10 at p. 3.

Applicants have accordingly amended claims 74 and 75 to recite "said plant is a tomato plant" and "said plant is a potato plant", respectively. Applicants thank the Examiner for the suggestion.

DOUBLE PATENTING

The Examiner states:

> Claim 73 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-5 of U.S. Patent No. 5,612,487.
>
> Claims 73-75 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-11 of U.S. Patent No. 6,034,298.
>
> Claims 73-75 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-51 and 56 of copending Application No. 09/918,937. This is a provisional of obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Id. at pp. 3-4.

Applicants are herein submitting Terminal Disclaimers (e.g., Terminal Disclaimer To Obviate A Provisional Double Patenting Rejection Over A Pending Second Application and Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent) wherein all the conflicting double patenting references are disclaimed therein.

Applicants are also herein submitting Exhibits to establish the chain of assignments for US Patent No. 5,612,487 from Edible Vaccines, Inc. to Terramed, Inc., which is now known as Prodigene, Inc. An assignment from Edible Vaccine, Inc. to Terramed, Inc. was recorded in the PTO at Reel/Frame 011265/0074 on October 24, 2000 (see Exhibit A). Also enclosed, designated as Exhibit B, is proof of change of name established by the attached certificate of the Secretary of State of Texas showing the name change of Terramed, Inc. to Prodigene, Inc. Furthermore, submitted herein is a copy of the "Recordation Form Cover Sheet" and "Patent License and Assignment Agreement" between Edible Vaccines, Inc. and Terramed, Inc, submitted to the Patent Office (see Exhibit C).

Common Ownership:

Additionally, the undersigned states:

US Patent No. 5,612,487 was at the time the invention was made, owned by, or subject to an obligation of assignment to Edible Vaccines, Inc. now known as Prodigene, Inc. (See Exhibits).

US Patent No. 6,034,298 was at the time the invention was made, owned by, or subject to an obligation of assignment to Prodigene, Inc.

Application Serial Nos. 09/918,937 and 09/816,846 were at the time the invention was made, owned by, or subject to an obligation of assignment to Prodigene, Inc.

In view of the Terminal Disclaimers, Applicants respectfully request this rejection be withdrawn.

The Examiner further states:

> Claim 73 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 73 of copending Application No. 09/816,846. Although the conflicting claims are not identical, they are not patentably distinct from each other because all claims are drawn to methods of producing a viral antigen (i.e. vaccine/immunogen) in transgenic plants. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In view of the Terminal Disclaimer filed herein (see above), Applicants respectfully request this rejection be withdrawn.

CLAIM REJECTIONS - 35 U.S.C. §102

Claims 73-74 are rejected under 35 U.S.C. § 102(b) as being anticipated by Goodman et al. (WO 87/00865).

The Examiner states:

> Goodman et al. discloses the use of transgenic plants to express recombinant viral antigen proteins from leukemia and lymphotrophic retroviruses, herpes simplex virus, hepatitis B virus and adenovirus. Goodman et al. further discloses the use of tomato plants, as well as other edible plants, to express said proteins. The

> methodology disclosed by Goodman et al. comprises constructing a plasmid vector comprising the polynucleotide encoding the protein (viral antigen) coupled to a promoter that is functional in the plant host; transferring said plasmid vector to a plant cell; the regeneration of said plant from the transformed cells; the harvest of the plants or plant parts to obtain the expressed viral antigen protein; and the purification of said antigen protein. Consequently, Goodman et al. anticipates all the limitations of the rejected claims.

Id. at pp. 5-6.

For anticipation to exist, one must disclose in the related art reference each and every claim limitation found in Applicants' claims.

Applicants have amended claim 73 to recite "harvesting a portion of said regenerated transgenic plant, said portion containing said expressed immunogenic viral antigen, wherein said expressed antigen causes stimulates an immune response". This is distinguishable from Goodman WO 87/00865 because Goodman merely discloses that the proteins produced by their method be "physiologically active". One of skill in the art would likely understand physiologically active to mean that the protein folds correctly and has some biological activity or relate it to the proteins effect on metabolism post consumption; however, many protein antigens are not intrinsically immunogenic, particularly as a vaccine. Physiologically active peptides and antigens or immunogens are different because immunogenic peptides contain epitopes that are useful in inducing immune responses. A protein antigen is not necessarily immunogenic unless an immunogenic region is present that is accessible to the antibody-forming mechanism. The constructs of Goodman which encodes physiologically active proteins, such as interferon, are mediators which go to helping regulate the growth and function of active cells. Goodman does not disclose that the physiologically active peptides have any immunoregulatory functions, which are highly desirable for a vaccine.

Moreover, Goodman discloses the production of primarily digestive enzymes (See pg. 9, line 37 to pg. 10, lines 1-4 of WO 87/00865) in plants and notes that these recombinant enzymes retain physiologic activity when purified from the plant. In other words these enzymes maintain their original physiological activities; are properly folded, etc. and remain catalytically active. A protein that retains physiologic activity may not necessarily have immunogenic activity if the epitope is not conserved. Further, in 1988 at the time of the Goodman reference, the state of the art was such that when an antigen expressed in a plant was consumed by an animal it was unknown whether it would be either digested or not presented to the immune system to allow for recognition. Presented herewith for the Examiner's review is an article from *Science* September 1994 which discusses the problems encountered with oral vaccines, an excerpt of which follows:

> Mucosal vaccine researchers have been stymied before during the decades they've been working on these preparations, and many of the same obstacles remain. Despite early successes with live attenuated oral vaccines against tuberculosis and polio more than 30 years ago, the expected heyday for mucosal vaccines never followed. One problem was that the chemical attenuation methods then in use altered the genes and pathogens randomly, in many cases changing them enough so that they failed to trigger a vigorous immune response. Other mucosal vaccines, which are usually ingested orally, inhaled, or taken as nose drops, fell victim to destruction by bodily defenses such as enzymes and acids in the stomach, problems not faced by serum vaccines...

Service, Robert F., Research News, *Science* 263:1522-1524 "Triggering the First Line of Defense" (1994).

Thus, art-recognized problems associated with oral vaccines are not taken into account in Goodman. Critical to achieving vaccine activity is expression of the antigen at levels necessary to provide for an immune response. The levels of expression disclosed in Goodman would not be high enough to achieve the response contemplate by Applicant's invention.

Claim 73-74 are rejected under 35 U.S.C. § 102(e) as being anticipated by Goodman et al. (U.S. Patent No. 4,956,282).

The Examiner states:

> Goodman et al. discloses the use of transgenic plants to express recombinant viral antigen proteins from leukemia and lymphotrophic retroviruses, herpes simplex virus, hepatitis B virus and adenovirus. Goodman et al. further discloses the use of tomato plants, as well as other edible plants, to express said proteins. The methodology disclosed by Goodman et al. comprises: constructing a plasmid vector comprising the polynucleotide encoding the protein (viral antigen) coupled to a promoter that is functional in the plant host; transferring said plasmid vector to the plant cell; the regeneration of said plant from the transformed cells; the harvest of the plants or plant parts to obtain the expressed viral antigen protein; and the purification of said antigen protein. Consequently, Goodman et al. anticipate all the limitations of the rejected claims.

Id. at pp. 6-7.

Applicants have amended claim 73 to recite "harvesting a portion of said regenerated transgenic plant, said portion containing said expressed immunogenic viral antigen, wherein said expressed antigen causes stimulates an immune response". This is distinguishable from Goodman U.S. Patent No. 4,956,282 because Goodman not only recites that the proteins produced be physiologically active, but also is directed to the production of primarily digestive enzymes (see col. 1, lines 64-67). One of skill in the art would likely understand physiologically active to mean that the protein folds correctly and has some biological activity or even to the proteins effect on metabolism post consumption; however, not necessarily be immunogenic (see page 3, lines 5-7) or capable of eliciting an immune response, particularly as a vaccine. A protein or antigen is not necessarily immunogenic unless an immunogenic region is present that is accessible to the antibody-forming mechanism. Goodman fails to show that the constructs induce systemic and mucosal antibody responses, which are highly desirable for a vaccine.

Goodman discloses the production of primarily digestive enzymes (See col. 5, lines 55-60) in plants and notes that these recombinant enzymes retain physiologic activity when purified from the plant. In other words these enzymes maintain their

original physiological activities; are properly folded, etc. and remain catalytically active. A protein that retains physiologic activity may not necessarily retain immunogenic activity if the epitope is not conserved. As stated above, in 1988 at the time of the Goodman reference, the state of the art was such that when an antigen expressed in a plant was consumed by an animal it was unknown whether it would be either digested or not presented to the immune system to allow for recognition. Applicants respectfully direct Examiner's attention to the article from *Science* September 1994 which discusses the problems encountered with oral vaccines. Thus, art-recognized problems associated with oral vaccines are not taken into account in Goodman. Critical to achieving vaccine activity is expression of the antigen at levels necessary to provide for an immune response. The levels of expression disclosed in Goodman would not be high enough to achieve the response contemplate by Applicant's invention.

CLAIM REJECTIONS - 35 U.S.C. §103

Claim 75 is rejected under 35 U.S.C. §103(a) as being unpatentable over Goodman et al. (WO 87/00865).

The Examiner states in part:

> Goodman et al. discloses the use of transgenic plants to express recombinant viral antigen proteins from leukemia and lymphotrophic retroviruses, herpes simplex virus, hepatitis B virus and adenovirus. Goodman et al. further discloses the use of tomato plants, as well as other edible plants, to express said proteins.

The methodology disclosed by Goodman et al. is described *supra*. The Examiner further states:

> Goodman et al. differs from the claimed invention in that they do not explicitly disclose the use of potato plants as the recipients of the plasmid vector. However, since Goodman et al. discloses the use of tomato and tobacco plants to express said proteins and tomato, potato and tobacco plants are all members of the same

> phylogenic family (*Solanaciai*), the use of potato plants merely constitutes an obvious variation of the method disclosed in the cited reference. One of skill in the art would have a high expectation of success since potato plants are very similar to the disclosed tomato and tobacco plants. Moreover, Goodman et al. discloses that the recombinantly expressed protein could be found in plant parts such as tubers.

Id. at pp. 7-9.

Applicants respectfully submit the Examiner must show some objective teaching leading to this modification to avoid hindsight. When obviousness is based on a particular [related] reference, there must be a showing of a suggestion or motivation to modify the teaching of that reference to get to the claimed invention. *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582 (Fed. Cir. 1996). Moreover, the showing must be clear and particular (see e.g., *C.R. Bard v. M3 Systems, Inc.*, 157 F.3d 1340, 1352).

Applicants respectfully submit there is no suggestion in Goodman that it be modified is the manner suggested by the Examiner. Absent such a suggestion, there would be no reason why one skilled in the art who was faced with the same problem confronting the Applicants and who had no prior knowledge of Applicant's claimed method would consult this reference as suggested by the Examiner. Goodman et al. shows no recognition to, or pertinence to a protein having and even more importantly maintaining immunogenic activity, particularly if the epitope is not conserved. The Goodman reference discloses the production of primarily digestive enzymes (See pg. 9, line 37 to pg. 10, lines 1-4 of WO 87/00865) in plants and notes that these recombinant enzymes retain physiologic activity when purified from the plant. In other words these enzymes maintain their original physiological activities; are properly folded, etc. and remain catalytically active. A protein that retains physiologic activity may not necessarily retain immunogenic activity if the epitope is not conserved. Further, in 1988 at the time of the Goodman reference the state of the art was such that when an antigen expressed in a plant was consumed by an

animal it was unknown whether it would be either digested or not presented to the immune system to allow for recognition. Presented herewith for the Examiner's review is an article from *Science* September 1994 which discusses the problems encountered with oral vaccines, an excerpt of which follows:

> Mucosal vaccine researchers have been stymied before during the decades they've been working on these preparations, and many of the same obstacles remain. Despite early successes with live attenuated oral vaccines against tuberculosis and polio more than 30 years ago, the expected heyday for mucosal vaccines never followed. One problem was that the chemical attenuation methods then in use altered the genes and pathogens randomly, in many cases changing them enough so that they failed to trigger a vigorous immune response. Other mucosal vaccines, which are usually ingested orally, inhaled, or taken as nose drops, fell victim to destruction by bodily defenses such as enzymes and acids in the stomach, problems not faced by serum vaccines...

Service, Robert F., Research News, *Science* 263:1522-1524 "Triggering the First Line of Defense" (1994).

Thus, art-recognized problems associated with oral vaccines are not taken into account in Goodman. Critical to achieving vaccine activity is expression of the antigen at levels necessary to provide for an immune response. The levels of expression disclosed in Goodman would not be high enough to achieve the response contemplate by Applicant's invention. Therefore, Applicants respectfully request this rejection be withdrawn.

Claim 75 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Goodman et al. (U.S. Patent No. 4,956,282).

The Examiner states:

> Goodman et al. discloses the use of transgenic plants to express recombinant viral antigen proteins from leukemia and lymphotrophic retroviruses, herpes simplex virus, hepatitis B virus and adenovirus. Goodman et al. further discloses the use of tomato plants, as well as other edible plants, to express said proteins.

The methodology disclosed by Goodman et al. is described above. The Examiner further states:

> Goodman et al. differs from the claimed invention in that they do not explicitly disclose the use of potato plants as the recipients of the plasmid vector. However, since Goodman et al. discloses the use of tomato and tobacco plants to express said proteins and tomato, potato and tobacco plants are all members of the same phylogenic family (*Solanaciai*), the use of potato plants merely constitutes an obvious variation of the method disclosed in the cited reference. One of skill in the art would have had a high expectation of success since potato plants are very similar to the disclosed tomato and tobacco plants. Moreover, Goodman et al. discloses that the recombinantly expressed protein could be found in plant parts such as tubers.

Id. at pp. 9-10.

Applicants respectfully submit there is no suggestion in Goodman that it be modified is the manner suggested by the Examiner. Absent such a suggestion, there would be no reason why one skilled in the art who was faced with the same problem confronting the Applicants and who had no prior knowledge of Applicant's claimed method would consult this reference as suggested by the Examiner. Goodman et al. shows no recognition to, or pertinence to a protein having and even more importantly maintaining immunogenic activity, particularly if the epitope is not conserved. The Goodman reference discloses the production of primarily digestive enzymes (See col. 5, lines 55-60 of US Patent No. 4, 956,282) in plants and notes that these recombinant enzymes retain physiologic activity when purified from the plant. In other words these enzymes maintain their original physiological activities; are properly folded, etc. and remain catalytically active. However, as stated previously, a protein that retains physiologic activity may not necessarily retain immunogenic activity if the epitope is not conserved. Further, in 1988 at the time of the Goodman reference the state of the art was such when that an antigen expressed in a plant was consumed by an animal it was unknown whether it would be either digested or not presented to the immune system to allow for recognition. Applicants respectfully direct

Examiner's attention to the article from *Science* September 1994 which discusses the problems encountered with oral vaccines. An excerpt is presented *supra.*

Thus, Goodman has not taken into account art-recognized problems associated with oral vaccines. Critical to achieving vaccine activity is expression of the antigen at levels necessary to provide for an immune response. The levels of expression disclosed in Goodman would not be high enough to achieve the response contemplate by Applicant's invention. Thus, Applicants respectfully request this rejection be withdrawn.

CONCLUSION

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a response in the above identified application for 2 months from December 26, 2003 to February 26, 2004.

Applicant is a small entity under 37 CFR 1.9 and 1.27. A small entity statement under 37 CFR 1.27 has already been filed in this application.

Enclosed is our check in the amount of $210.00 to cover the cost of the extension. Any deficiency or overpayment should be charged or credited to Deposit Account 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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- pw/tyb/bja -